REMARKS

Claims 1, 3, 4 and 9-14 are pending in this application. The Office Action withdraws claims 11-14 as drawn to a non-elected invention due to constructive election by original presentation; and rejects claims 1, 3, 4, 9 and 10 under 35 U.S.C. §103(a). In view of the following remarks, reconsideration and allowance are respectfully requested.

I. Restriction

Claims 11-14 are withdrawn by the Office Action as directed to a non-elected invention due to constructive election through original presentation. Applicants respectfully traverse the restriction.

The Restriction Requirement is traversed because claims 1, 3, 4, 9, 10 and 11-14 are drawn to sufficiently interrelated inventions to warrant examination thereof in a single application. Claims 1, 3, 4, 9 and 10 are drawn to a pharmaceutical composition, while claims 11-14 are drawn to methods of using that pharmaceutical composition.

Where product and process claims are presented in the same application, Applicant may be called upon under 35 U.S.C. §121 to elect claims to either the product or process. MPEP §821.04. However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim depends from or otherwise includes all the limitations of an allowed product claim. *Id.*

In the present application, the method claims 11-14 include all of the limitations of the product of claims 1, 3, 4, 9 and 10. In particular, all of the limitations of the independent product claim 1 are incorporated into the methods of claims 11-14.

Since the method claims include the limitations of the product claims, the method claims must be rejoined with the product claims once the product claims are allowed. Thus, to streamline prosecution and avoid delay, the Restriction Requirement should be withdrawn to

permit concurrent examination of all of the pending claims. Applicants respectfully request reconsideration and withdrawal of the Restriction Requirement.

It is also respectfully submitted that the subject matter of all pending claims is sufficiently related that a thorough search for the subject matter of any one Group of claims would encompass a search for the subject matter of the remaining claims. Thus, it is respectfully submitted that the search and examination of the entire application could be made without serious burden. See MPEP §803 in which it is stated that "if the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions" (emphasis added). It is respectfully submitted that this policy should apply in the present application in order to avoid unnecessary delay and expense to Applicants and duplicative examination by the Patent Office.

Thus, withdrawal of the Restriction Requirement is respectfully requested.

II. Rejection Under 35 U.S.C. §103(a)

Claims 1, 3, 4, 9 and 10 are rejected under 35 U.S.C. §103(a) as having been obvious over Kumagai (U.S. Patent Application Publication No. 2002/0115622) in view of Koga ("Preparation and Rectal Absorption of Highly Concentrated Glycyrrhizin Solution", Biol. Pharm. Bull., 2003, 26(9) p. 1299-1305) and Mollica ("Stability of Pharmaceuticals", Journal of Pharmaceutical Sciences, 1978, 67(4), p. 443-465). Applicants respectfully traverse the rejection.

The Office Action fails to establish a *prima facie* case of obviousness because the applied references fail to teach or suggest every limitation of independent claims 1 and 10. Accordingly, the applied references, alone or in combination, would not have rendered obvious independent claims 1 and 10 and the claims dependent therefrom.

A. Kumagai

Independent claim 1 recites, in part, "8 to 16 mg/mL of glycyrrhizin, 3 to 6 mg/mL of cysteine and 80 to 160 mg/mL aminoacetic acid, wherein substantially no sulfite is contained." Similarly, independent claim 10 recites, in part, "8 to 16 mg/mL (as glycyrrhizin) of monoammonium glycyrrhizinate, 4 to 8 mg/mL of cysteine hydrochloride and 80 to 160 mg/mL aminoacetic acid, wherein substantially no sulfite is contained." As Applicants previously argued in the Amendment filed on December 3, 2007 ("December 3 Amendment"), Kumagai's disclosure of a pharmaceutical composition comprising 2 mg/mL glycyrrhizin ammonium salt, 1 mg/mL cysteine hydrochloride and 20 mg/mL aminoacetic acid would not have rendered the claimed inventions obvious.

Page 7 of the Office Action mischaracterizes the argument presented in the December 3 Amendment by indicating that in that Amendment, "Applicant[s argued] the *criticality* of the concentration of the invention by showing that the claimed range achieves unexpected results" (emphasis added). However, as indicated on page 8 of the December 3 Amendment, under MPEP §2144.05(I), where the claimed ranges and prior art ranges do not overlap, as is the case in the claimed invention and Kumagai, the test for determining obviousness is not whether the range is "critical" but whether the two non-overlapping ranges are "close enough that one skilled in the art would have expected them to have the same properties."

Accordingly, as indicated on page 8, first and second paragraphs of the December 3 Amendment, Kumagai would not have rendered obvious the claimed invention because the non-overlapping ranges are not "close" as that term has been interpreted by the case law. Specifically, in *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) "close" is a difference of 0.05% in concentration. Here, the concentrations differ by at least 300%, and can differ by up to 800%. Clearly, in the field of pharmaceutical

compositions as in the claimed inventions and Kumagai, concentrations that differ by as much as 300-800% are not "close" such that one of ordinary skill in the art would have expected the respective compositions to have the same properties. Instead, the concentrations of the present invention and Kumagai are vastly different.

Furthermore, as indicated on page 8, third paragraph to page 9, end of first full paragraph of the December 3 Amendment, in light of such vast difference in concentrations between the claimed invention and Kumagai: 1) one of ordinary skill in the art would not have expected the claimed compositions and the composition of Kumagai to exhibit the same properties, and 2) experimental data supports that the compositions, in fact, do not exhibit the same properties. This showing is further indicative that the non-overlapping ranges of the claimed invention and Kumagai are not close enough that one skilled in the art would have expected them to have the same properties under the test for determining obviousness as established by case law. Accordingly, Applicants have properly established that Kumagai would not have rendered the claimed invention obvious by establishing that the claimed ranges and Kumagai's ranges are not "close enough that one skilled in the art would have expected them to have the same properties," and not by establishing that the claimed range is "critical," as the Office Action incorrectly alleges. For at least this reason, Kumagai's ranges would not have rendered the claimed invention obvious.

Moreover, as page 5 of the Office Action admits, Kumagai fails to teach or suggest a composition "wherein substantially no sulfite is contained," as recited by independent claims 1 and 10. Therefore, for at least this additional reason, Kumagai's ranges would not have rendered the claimed invention obvious. Applicants respectfully request reconsideration and withdrawal of the rejection.

B. Koga

Pages 5 and 7 of the Office Action relies on Koga for providing "evidence that it is an expected result that an increased concentration of glycyrrhizin remains soluble, or stable, when in the presence of increased concentration of buffer (page 1301, right column, lines 4-10)" and that because "[c]ysteine hydrochloride and aminoacetic acid function as buffers, therefore it is expected that an increased concentration of glycyrrhizin [as compared to conventional concentrations] would remain soluble in the presence of increased concentration of buffers [as compared to conventional concentrations]." However, not only is this assertion unsubstantiated, but it is also contrary to actual experimental results disclosed in the present specification. Therefore, the Office Action fails to establish that Koga, alone or in combination with Kumagai, would have rendered the claimed invention obvious.

First, the Office Action's assertion is unsubstantiated because it is based on a mischaracterization of Koga's teachings. At most, Koga teaches that "increased *phosphate* buffer concentration improved GZ [glycyrrhizin] solubility" (emphasis added). See page 1301, right column, lines 4-10 of Koga. Koga discusses specifically the effect of *phosphate buffer* on glycyrrhizin solubility, but nowhere in Koga is the effect of cysteine and aminoacetic acid, as recited in claims 1, and cysteine hydrochloride and aminoacetic acid, as recited in claim 10, described. In fact, Koga is silent as to the effect of *any* other substance (buffer or non-buffer), other than phosphate buffer, on glycyrrhizin solubility. Therefore, Koga provides no reason or rationale for one of ordinary skill in the art to have deduced from its disclosure that including 3 to 6 mg/ mL of cysteine and 80 to 160 mg/mL of aminoacetic acid (as recited by claim 1), or 4 to 8 mg/mL of cysteine hydrochloride and 80 to 160 mg/mL of aminoacetic acid, (as recited by claim 10), to a compound containing 8 to 16 mg/ mL of glycyrrhizin would improve glycyrrhizin solubility. Accordingly, for at least this reason, Koga would not have rendered the claimed invention obvious.

Additionally, Example 1 and Table 1 of the present specification clearly disproves the Office Action's asserted theory that "[c]ysteine hydrochloride and aminoacetic acid function as buffers, [and] therefore it is expected that an increased concentration of glycyrrhizin [over conventional concentrations] would remain soluble in the presence of increased concentration of buffers [over conventional concentrations]." According to the Office Action's theory, the presence of cysteine hydrochloride and aminoacetic acid in the claimed concentrations alone should act as a sufficient stabilizer, and thus should prevent glycyrrhizinate precipitation and cysteine degradation. However, Example 1 shows that when 2.4 or 4.0 mg/mL of sodium sulfite is added to the cysteine hydrochloride and aminoacetic acid in the claimed concentrations, glycyrrhizinate precipitation still results. Therefore, contrary to the Office Action's assertions, glycyrrhizin did not remain soluble in the presence of cysteine hydrochloride and aminoacetic acid in the claimed concentrations. Accordingly, because the obviousness rejection of the present claims over Kumagai in view of Koga is premised on a flawed rationale, the Office Action fails to establish a *prima facie* case of obviousness of the claimed inventions in view Kogo, alone or in combination. Reconsideration and withdrawal of the rejection are respectfully requested.

C. Mollica

Pages 5-6 of the Office Action relies on Mollica only for its alleged teaching omitting sodium sulfite based on Mollica's teaching that "undesired 'extrachemical reactions' *can* occur when stabilizing excipients are added to drug formulations" (emphasis added), specifically that "sodium bisulfite can cause precipitation of the drug from the formulation." However, at most, page 449, left column, lines 2-3 of Mollica describes that "Sodium bisulfate can cause precipitation of imipramine hydrochloride." Mollica nowhere teaches that sulfites cause precipitation of glycyrrhizin, and thus that substantially no sulfite is included as required by the claimed invention.

At most, Mollica provides a reason or rationale to one of ordinary skill in the art to omit sodium bisulfite in a compound containing imipramine hydrochloride, but it fails to provide a reason or rationale to omit sodium bisulfate from a compound containing glycyrrhizin. Accordingly, a person having ordinary skill in the art could not have modified the teachings of Kumagai, Koga, and Mollica so as to produce the presently claimed pharmaceutical solution comprising glycyrrhizin, cysteine and aminoacetic acid, wherein substantially no sulfite is contained, because Mollica does not teach or suggest any specific predictable effect of sulfites on these specific compounds. Thus, the elimination of sulfites would not have been obvious.

Therefore, the presently claimed inventions would not have been obvious because, again, Kumagai teaches the inclusion of sulfites; Koga merely teaches the behavior of glycyrrhizin in the presence of phosphate buffers, but not in the presence of glycyrrhizin, cysteine (or cysteine hydrochloride) or aminoacetic acid; and Mollica does not teach any relationship between sulfites and the presently recited compounds (only the relationship between sulfites and other, unrelated, compounds). Thus, the presently claimed pharmaceutical composition comprising glycyrrhizin, cysteine (or cystein hydrochloride) and aminoacetic acid, wherein substantially no sulfite is contained would not have been obvious over the cited references.

Independent claims 1 and 10 are therefore patentable over the cited references, for at least the reasons discussed above. Dependent claims 3, 4 and 9 are therefore also patentable for at least the reason that independent claim 1 is patentable.

Reconsideration and withdrawal of the rejection are respectfully requested.

III. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the

Respectfully submitted,

James A. Oliff
Registration No. 27,075

Hee H. Smith
Registration No. 57,631

JAO:HHS/caa

Date: August 7, 2008

OLIFF & BERRIDGE, PLC
P.O. Box 320850
Alexandria, Virginia 22320-4850
Telephone: (703) 836-6400

DEPOSIT ACCOUNT USE AUTHORIZATION
Please grant any extension necessary for entry;
Charge any fee due to our Deposit Account No. 15-0461